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FKBP51 and FKBP52 as potential biomarkers for predicting endometrial receptivity and embryo implantation in assisted reproductive technologies

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Abstract

One of the most important and limiting factors in assisted reproductive technologies (ART) is repeated implantation failure (RIF). In the process of embryo implantation, appropriate function of the progesterone hormone through its receptors is critical for establishment of a receptive endometrium. FKBP51 and FKBP52 are two co-chaperones of progesterone receptors that participate in the progesterone signaling pathway and endometrial receptivity. These 51 and 52 KD proteins increase and decrease the affinity of progesterone hormone receptors to their ligand, respectively. The endometrial tissue of RIF patients might have different patterns of FKBP51 and FKBP52 gene expression. These molecules can easily be detected and quantified by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) and immunohistochemical (IHC) studies. Assessment of these molecules could be a valuable method for evaluation of endometrial receptivity and prediction of the implantation and pregnancy outcome before beginning a treatment cycle for RIF patients in ART procedures.

Keywords: ART, Repeated implantation failure, Progesterone, FKBP51, FKBP52

1. Introduction

Today's assisted reproductive technologies (ART), such as IUI, IVF and ICSI, are widely used for treatment of infertile couples worldwide and many children have been born through ART. However, despite many improvements in these technologies the success rate is limited to around 25-30% (1). In many IVF cycles, despite selection and transferring good quality embryo, implantation does not occur, so many of infertile couples experience repeated implantation failure, the most important limiting factor in ART (2). In the process of implantation, uterine receptivity, which limited to time between days 19-24 in a normal menstrual cycle and called "window of implantation," is a critical factor.

Progesterone has a key role in preparing the endometrium for accepting the embryo. So any factors contributing to the progesterone hormone's signaling pathway determined relevant to endometrial receptivity, and inappropriate changes in these factors, lead to implantation deficiency (3-6).

We provide evidence that altered expression of some special co-chaperones, contributed in progesterone hormone receptors, causes progesterone resistance and some gynaecological problems in both human and animal models.

2. Hypothesis

Having been shown in some studies, the genetic profile and gene expression of endometrial tissue in

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RIF women is different from that of normal women with history of pregnancy and live births, so determining possible biomarkers of a receptive endometrial tissue has special importance to further improving implantation rates in ART. We hypothesise that evaluation of the gene expression of two immunophilins, FKBP51 and FKBP52, as progesterone receptor co-chaperones and related to progesterone hormone signaling can be used as candidate biomarkers of endometrial receptivity, endometrial response to progesterone and also predicting embryo implantation and pregnancy outcome in ART. We can measure these two factors prior to introducing patients to expensive and complicated ART procedures.

Evaluation of the hypothesis

In order to evaluate this hypothesis, we provide some evidence based on the studies conducted thus far:

(1) The function of the progesterone hormone is crucial for establishment of a receptive endometrium and embryo implantation.

(2) FKBP51 and FKBP52 participate in the cellular response of endometrial tissue to progesterone.

(3) Altered expression of FKBP51 and FKBP52 genes leads to some gynecological conditions.

3. FKBP51 and FKBP52

FK506 binding proteins (FKbps) are members of the peptidyl prolyl cis/trans isomerases (PPIase) superfamily found in all organisms from archaebacteria to primates and participate in the protein folding process and specially signal transduction (7-9). PPIase molecules catalyse cis/trans isomerisation of the imide peptidyl-prolyl bonds.[10] To date families of PPIase have been divided into cyclophilins, FKBPs and parvulins (11, 12). Cyclophilins and FKBPs are called immunophilins due to their ability to bind to immunosuppressive drugs, cyclosporin A and FK506 or rapamycin, respectively, by their PPIase domain and mediating the action of these drugs (13).

Some members of the FKBP and Cyp families contain a tetratricopeptide repeat (TPR) domain that binds to the C-terminal end of heat shock protein 90 (Hsp90), a key protein in steroid hormones complex that interacts directly with the hormone-binding domain of the receptor (14, 15).

Steroid receptors are soluble proteins trafficking between cytoplasm and nucleus. In the absence of hormone, steroid receptors are in a complex with some other molecules such as HSP90 and are kept inactivated. After binding of receptor to steroid hormone, receptor dissociates from complex and enter the nucleus, dimers and act as transcription factor (12).

FKBP51 and FKBP52, 51 and 52 kDa FK506-binding proteins, are two immunophilins characterized as Hsp90-binding co-chaperones with conserved TPR domain, which were first identified in complex with steroid hormone receptors (16). Since discovery of these two immunophilins about 20 years ago, their function in regulation of signaling pathways of steroid hormone receptors and endocrine-related physiological processes have been widely studied (16). FKBP51 has the alternate names FKBP54 and p54, and FKBP52 carries alternate names FKBP59, HBI, p50 and HSP56 (16-18). Although these HSP90 co-chaperones have 70% similarity in their structures, functionally they are different (19-20). They have a common binding site on Hsp90 and compete for binding to steroid hormone receptors so that the high expression of FKBP51 gene attenuates the function of receptor by FKBP52 (21).

Studies showed that FKBP52 is a positive regulator for glucocorticoid, progesterone and androgen receptors while FKBP51 is a negative regulator of steroid receptors (21-25). In the progesterone hormone signaling pathway, FKBP52 elevates the hormone binding affinity of progesterone receptor while FKBP51 decreases this affinity and attenuates the response of target cell to progesterone hormone (21-26).

Nowadays these two co-chaperones are considered the therapeutic targets for various kinds of endocrine-related diseases, such as prostate and breast cancer, metabolic diseases and neurological disorders. Male and female contraceptive drugs are among the scientific and industrial researches being conducted on these two immunophilins (27-31).

4. Role of FKBP51 and FKBP52 in male and female reproductive systems

Male knockout mice for FKBP52 have androgen insensitivity and display some phenotypes such as dysgenesis of prostate and seminal vesicle, ambiguous external genitalia and hypospadias (24, 32-34). Lower number of epididymal sperm and also lower number of sperm with normal morphology and motility and even azoospermic phenotype are seen in male mice with FKBP52 deficiency (35, 36). Altered expression of these two immunophilins as co-chaperones of the androgen receptor has been seen in prostate hyperplasia and cancer (27, 37-42).

Higher level of FKBP51 gene expression in decidual cells of pregnant women facilitates their

labor process by reducing sensitivity of these cells to progesterone, indicating its contribution to progesterone signaling pathway and response of target tissues to progesteroneIn (43). Deficiency of FKBP52 expression is related to clinical manifestation of endometriosis in humans, mice and baboons, ovarian anomaly, lack of breast development, attenuated ovulation, decidualisation disorders, pregnancy failure, and decrease in transcription of steroidogenic enzymes, all caused by progesterone resistance (44-48). In addition, knockout of the FKBP52 gene in female mice leads to aberrant embryo implantation as the result of progesterone insensitivity of endometrial tissue and downregulation of genes regulated by progesterone 14, 49). Studies showed that expression of FKBP52 gene in endometrial tissue of women with unexplained infertility is decreased (44). Also it has been suggested that assessment of FKBP52 gene and protein expression is positively related to ultrasonic evaluation of endometrial receptivity and his immunophilin may have an important role in improving the receptivity of endometrium (50).

5. Discussion

The biggest problem in ART is repeated implantation failure as the result of low embryo quality or a nonreceptive endometrium. Prediction of the endometrial receptivity and its response to progesterone hormone helps us manage RIF patients more appropriately. In this hypothesis, we provided evidence that altered expression of FKBP51 and FKBP52 in endometrial tissue is related to progesterone insensitivity.

According to this hypothesis upregulation of FKBP51 and downregulation of FKBP52 in endometrial tissue result in progesterone resistance, insufficient response of this tissue to progesterone hormone, attenuated endometrial receptivity, implantation failure and, finally, infertility. This hypothesis can be evaluated by measuring the levels of FKBP51 and FKBP52 gene and protein expression using qRT-PCR and IHC techniques respectively, in endometrial tissue of RIF versus normal women in mid-secretory phase of menstrual cycle named “window of implantation”.

Therefore, this hypothesis introduces FKBP51 and FKBP52 as new biomarkers for evaluation of endometrial receptivity and prediction of patient response to ART procedures and also ART outcome.

For prediction of endometrial response and ART outcome using these biomarkers, endometrial biopsy should be done in mid-secretory phase of menstrual cycle prior to beginning ART procedures for these patients.

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